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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,280	05/05/2005	Bernat Vidal Juan	09605-.0002	7655

22852 7590 02/27/2007

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EXAMINER	
MOORE, SUSANNA	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,280	VIDAL JUAN ET AL.	
	Examiner	Art Unit	
	Susanna Moore	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: SUBSTITUTED 4-(PYRROLO PYRIMIDIN-6-YL)BENZENESULPHONAMIDE DERIVATIVES.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 is drawn to a process of making compound of formula (II) from a compound of formula IV but does not recite the reagents needed to complete the reaction. The Examiner suggests adding back "by reaction with an excess of chlorosulphonic acid" which was removed by amendment.

Claims 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There are several kinds of diabetes, e.g. type I, type II, gestational diabetes and diabetes insipidus. Does Applicant intend one or all types?

Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled. .

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(A) Breadth of claims.

(a) Scope of the compounds. The instant claim embraces hundreds of compounds with a pyrrolopyrimidine scaffold with a variety of substituents at four positions of the bicycle.

(b) Scope of the diseases covered. The instant claims are drawn to a method for treating a subject with a pathological condition or disease susceptible to amelioration by antagonism of A2A and/or A2B adenosine receptors, wherein said diseases are autoimmune diseases, inflammatory conditions, asthma, Alzheimer's disease, Parkinson's disease, Huntington chorea, Wilson's disease, bronchoconstriction, allergic diseases, hypertension, atherosclerosis, reperfusion injury, myocardial ischemia, retinopathy, gastrointestinal tract disorders, cell proliferation disorders and diabetes mellitus. The Scope encompasses also those diseases in the Specification on pages 1 and 30, which include Addison's disease, autoimmune hemolytic anemia, Crohn's disease, Goodpasture's syndrome, Graves disease, Hashimoto's thyroiditis, idiopathic thrombocytopenic purpura, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, pemphigus vulgaris, pernicious anemia, poststreptococcal glomerulonephdtis, psoriasis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, spontaneous infertility, and systemic lupus erythematosus. Some of the more broader diseases listed above will be discussed in more detail below.

Immunology is a broad branch of biomedical science that covers the study of all aspects of the immune system and deals with, among other things, the physiological functioning of the immune system. The immune system protects the body from potentially harmful substances by recognizing and responding to antigens. Antigens are foreign substances that invade the body, e.g. viruses, fungi, or bacteria. Non-living substances such as toxins , chemicals, drugs, and foreign particles (such as a splinter) are antigens, too.

The immune system is the body's defense against infectious organisms and other invaders. Through a series of steps called the immune response, the immune system attacks antigens, which are not recognized by the body, and are destroyed by the immune system.

The immune system is made up of a network of cells, tissues, and organs that work together to protect the body. The key organs of the immune system are thymus, spleen, bone marrow, lymph vessels, lymph nodes and secondary lymphatic tissues such as tonsils, adenoids, and skin.

The immune system has a series of dual natures, the most important of which is self/non-self recognition. Parts of the immune system are antigen-specific (they recognize and act against particular antigens), systemic (not confined to the initial infection site, but work throughout the body), and have memory (recognize and mount an even stronger attack to the same antigen the next time).

The immune system is often divided into two sections. One being innate immunity which is comprised of hereditary (always there) components that provide an immediate "first-line" of defense to continuously ward off pathogens.

The second is adaptive immunity, which is triggered when an antigen is detected. Several types of cells work together to recognize and respond to it. These cells trigger the B lymphocytes to produce antibodies. Antibodies are specialized proteins that lock onto specific antigens. Antibodies and antigens fit together like a key and a lock.

Although antibodies can recognize an antigen and lock onto it, they are not capable of destroying it without help. That is the job of the T cells. The T cells are part of the system that

destroys antigens that have been tagged by antibodies or cells that have been infected or somehow changed. T cells are also involved in helping signal other cells (like phagocytes) to do their jobs. This response takes days to develop, and so is not effective at preventing an initial invasion, but it will normally prevent any subsequent infection, and also aids in clearing up longer-lasting infections.

Sometimes a person is born with an overzealous immune system. When this occurs the immune system is intack and present but not working properly. In these cases, the immune system fails to properly distinguish between self and non-self, and attacks a part of the the body. Diseases which are associated with this type of disorder of the immune system are called autoimmune disorders.

Some examples of autoimmune disorders are as follows, but not limited to: acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid, aplastic anemia, autoimmune hepatitis, Coeliac disease, Crohn's disease, diabetes mellitus, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, lupus erythematosus, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, pemphigus, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia and Wegener's granulomatosis.

An inflammatory disease can be defined as a disease characterized by inflammation anywhere in the body. Inflammation is the body's first response to injury, e.g. trauma, infection

irritation, etc. This is a non-specific immune response. Inflammation has two main components - cellular and exudative.

The exudative component involves the movement of fluid, usually containing many important proteins such as fibrin and immunoglobulins (antibodies). Fibrinogen is important for clot formation and the prevention of further loss of blood. Immunoglobulins may act as specific or nonspecific *opsonins* facilitating thus the process of phagocytosis, or may participate in antibody-dependent cell-mediated cytotoxicity (ADCC) by which target cells are destroyed by killer cells. Blood vessels are dilated upstream of an infection (causing redness and heat) and constricted downstream while capillary permeability to the affected tissue is increased, resulting in a net loss of blood plasma into the tissue - giving rise to edema or swelling. The swelling distends the tissues, compresses nerve endings, and thus causes pain.

The cellular component involves the movement of white blood cells from blood vessels into the inflamed tissue. Professional phagocytes (neutrophils, eosinophils, monocytes and tissue macrophages) are essential performing phagocytosis, lymphocytes are involved in the specific immune responses, endothelial cell in the regulation of leukocyte emigration from the blood into inflamed tissue and platelets with mast cells in the production of early phase mediators.

For the possibility of surrounding tissue damage, inflammatory responses must be well ordered and controlled. The body must be able to act quickly in some situations, for example to reduce or stop the lost of blood, whereas tissue repair and reconstruction can begin a little later. Therefore, a wide variety of interconnected cellular and humoral (soluble) mechanisms are activated when tissue damage and infection occur. The body has the capacity to respond to both

minor injuries such as bruising, scratching, cuts, and abrasions, as well as to major injuries such as severe burns and amputation of limbs.

Some examples of inflammatory diseases are as followed, but not limited to: allergies, appendicitis, arteritis, arthritis, asthma, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, hepatitis, hidradentitis supparativa, ileitis, immune reconstitution inflammatory syndrome (IRIS), laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pelvic inflammatory disease (PID), pericarditis, peritonitis, pharynx, pleuritis, phlebitis, pneumonitis, protitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis and vulvitis.

Some more specific examples of inflammatory diseases are as followed, but not limited to: Alexander disease, Alper's disease, Alzheimer disease, Amyotrophic lateral sclerosis, ataxia telangietasia, Batten disease, Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington disease, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, Multiple sclerosis, multiple system atrophy, Parkinson disease, Peizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, Refsum's disease, Sandhoff's disease, Schilder's disease, spinal muscular atrophy, Steele-Richardson-Olszewski disease and Taves dorsalis.

Proliferative disorders. This term covers not only all cancers, but also covers

precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, pulmonary fibrosis, clonal proliferative disorders including the various Myelodysplastic Syndromes (the assorted Refractory Anemias, Ph-Chromosome-Negative Chronic Myelocytic Leukemia, Chronic Myelomonocytic Leukemia and Agnogenic Myeloid Metaplasia) and the Myeloproliferative Disorders (Chronic myelogenous leukaemia, which exists in adult and juvenile forms; Polycythemia vera;. Agnogenic myeloid metaplasia and Essential thrombocythemia). It includes certain types of abnormal wound healings. It covers numerous types of abnormal angiogenisis e.g. in certain eye diseases (such as neovascular glaucoma, diabetic retinopathy, retinopathy of prematurity, retrolental fibroplasias, and age-related and certain other types of macular degeneration), Rosacea, some neurodegenerations, respiratory distress in the premature infant, some problems in embryonic development, and atherosclerosis. It includes the myeloproliferative disorders (such as primary polycythemia, primary (essential) thrombocythemia, chronic myelogenous leukemia and myleofibrosis). Also included are numerous Plasma cell dyscrasias, such as Multiple myeloma, Smouldering Myeloma, monoclonal gammopathy of unknown significance (MGUS), solitary plasmacytoma of bone (SPB), asymptomatic myeloma, Waldenström's macroglobulinemia, Solitary extramedullary plasmacytoma, Primary Amyloidosis, POEMS syndrome, and the three heavy-chain diseases). It also includes an assortment of skin disorders, such as psoriasis, atopic dermatitis, allergic contact dermatitis, epidermolytic hyperkeratosis, palmoplantar Pustulosis, lichenified eczema, seborrhoeic dermatitis and the keratinization disorders (including assorted ichthyoses, keratosis

pilaris, keratosis follicularis, tylosis, "knuckle pads", corns, assorted callosities, and numerous keratinization disorders found in dogs and cats). Also included are LAM (Lymphangioleiomyomatosis, a smooth muscle proliferative disorder of the lungs) rheumatoid arthritis and even Alzheimer's Disease. Indeed, almost anything that the body grows --- skin, blood cells, nerves, plasma, muscles, the vascular network, can grow too fast, or in a manner too undifferentiated.

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenoearcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma,

transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple mycloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological:, uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli- . Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin:

malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above identified conditions.

Functional gastrointestinal disorders can be defined as any disease or disorder associated with the GI tract, which include the mouth, esophagus, stomach, intestines, rectum and anus. Other organs, such as the spleen, bile ducts, gall bladder, liver and pancreas, can also be a cause of gastrointestinal disorders. As recited, the scope of the claim can include, but is not limited to, tooth decay, periodontal disease, abscesses, canker sores, cold sores, oral cancer, gastroesophageal reflux disease, dysphagia, esophagus cancer, circopharyngeal incoordination, achalasia, diverticula, burning mouth syndrome, pancreas cancer, Crohn's disease, colon polyps, diverticular disease, intestinal parasites, salivary gland disease, sialhorria, dentigerous cyst, glossitis, benign migratory, Ludwig's Angina, Melkerson-Rosenthal Syndrome, xerostamia, Pierre-Robin Syndrome, diabetes, lactose intolerance, bruxism,ulcerative colitis, cystic fibrosis, pernicious anemia, tropical sprue, cirrhosis, Bassen-Kornzweig syndrome, pancreatitis, Shwachman-Diamond syndrome, anal cancer, acute pancreatitis, anal fissure, anal fistula, colorectal cancer, hemorrhoids, perirectal abscess, proctitis, rectal prolapse, functional constipation, liver cancer, diarrhea, ankyloglossia, Irritable Bowel Syndrome, functional dyspepsia, peptic ulcer, intussusception, Coeliac disease, Whipple's disease, lymphoma, incontinence, chronic pancreatitis, Hirschsprung's disease, infant regurgitation, biliary disorder, hemochromatosis, Wilson disease, tyrosinemia, alpha 1 antitrypsin defiency, glycogen storage

disease, primary sclerosing cholangitis, hepatitis A, hepatitis B, hepatitis C, Reyes's syndrome.

Diabetes mellitus is a disease in which the body does not produce or properly use insulin. Insulin is a hormone that is needed to convert sugar, starches and other food into energy needed for daily life. The cause of diabetes continues to be a mystery, although both genetics and environmental factors such as obesity and lack of exercise appear to play roles.

There are many types of diabetes. For example:

Type 1 diabetes: An autoimmune disorder, which results from the body's failure to produce insulin.

Type 2 diabetes: A metabolic disorder, which results from insulin resistance (a condition in which the body fails to properly use insulin), combined with relative insulin deficiency.

Gestational diabetes: Results from being pregnant. There is no known specific cause but it is believed the hormones of pregnancy reduce a woman's receptivity to insulin resulting in high blood sugar.

Diabetes insipidus: Results from increased urine production caused by inadequate secretion of vasopressin by the pituitary gland.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of

enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information on page 31 of the Specification shows 2 mg to 500 mg, but this is generic, the same for the many disorders covered by the Specification. Dosage should be reported in mg/kg of body weight over time. The dosage information is thus, incomplete. Thus, it is unclear if this is 2-500 mg per administration? Per day? Thus, there is no specific direction or guidance regarding a regimen or dosage effective for themany disorders found in Scope of diseases above.

(D) State of the Prior Art: These compounds are substituted pyrrolo[3,4-d]pyrimidines with a particular substitution at four positions on the bicycle. So far as the examiner is aware, no substituted pyrrolopyrimidines of any kind have been used for the treatment of any of the diseases listed above under the Scope.

(E) Working Examples: The invention is drawn to a method of ameliorating the A2A and/or A2B adenosine receptor and treating all the diseases listed under the Scope of diseases above. On pages 28-29 of the Specification two inhibition assays were completed with A2A and A2B receptor subtypes. There are several working examples for each receptor subtype on page 29. However, there are no animal tests for the treatment of any of the diseases listed under the Scope above.

(F) Skill of those in the art: Up-regulated immune system diseases are all different and challenging to treat and generally cannot be treated by any one drug. For instance, Reiter's syndrome can be treated with antibiotics, a property these compounds are not disclosed to have. Hashimoto's disease is treated with thyroxine, while multiple sclerosis is not treatable.

To date, there are no A2A or A2B antagonists used to treat Parkinson's disease patients or dyskinesias. Note that Parkinson's disease itself is not treatable, current therapies are directed only to symptom alleviation.

For a compound or genus to be effective against inflammation generally is contrary to the present understanding of medical science. It establishes that it is not reasonable for any agent to be able to treat inflammation generally. That is, the skill is so low that no compound effective generally against inflammatory disorders has ever been found. In terms of the individual inflammatory disorders, this is completely varied. It ranges from areas where the skill level is high, as in asthma, to ARDS, where the skill level is so low that there is no effective pharmacological treatment. The skill level varies all over the place for these disorders, because there is such a staggering range of them covered in the claims.

Currently, there is no treatment for Alzheimer's disease, per se. Currently the only medications offer relatively small symptomatic benefit for some patients but do not slow disease progression. For example, acetylcholinesterase inhibitors, (Aricept®, Cognex®, Exelon®, and Reminyl®), and voltage-dependent NMDA-antagonists, (Memantine), are the only two chemical treatments available, which have properties these compounds are not disclosed to have. Indeed, A2A or A2B is not currently even considered an important research area, and thus the skill level

in the art of A2A or A2B treatment for Alzheimer's disease is especially low. The Palmer TRENDS in Pharmacological Sciences 23(9) 426-433 September 2002 article on drug therapy for Alzheimer's Disease is likewise mentioned; it too makes no mention of CCR1.

The diseases and disorders listed above cannot be treated by any one drug. These are all different diseases and disorders, which occur at different locations and by different modes of action in the body. Rheumatoid arthritis, an inflammatory disease, itself can be treated only with compounds or drugs that directly suppress alpha tumor necrosis factor (TNF), e.g. Enbrel, Humira and Remicade. Applicants compounds are not disclosed to block alpha TNF, let alone is their evidence that they do. The skill of one in the art is such that only such agents have been made to work. Furthermore, currently there is no actual treatment for multiple sclerosis itself, only management of symptoms.

(G) The quantity of experimentation needed: Owing especially to factors A, C, E and F the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13, 15, 18 and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim1-20 and 22-28 of copending Application No. 10481728. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant Application is a subgenus of the copending Application 10481728.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SM

Brenda Coleman

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Primary examiner
Art Unit 1624
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